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AWARD NUMBER: W81XWH-14-1-0021

TITLE: A Pharmacokinetic/Pharmacodynamic Study of the Glucocorticoid Receptor Antagonist Mifepristone Combined with Enzalutamide in Castrate-Resistant Prostate Cancer

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14. ABSTRACT

This is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor (GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The first objective is, within the context of a phase I clinical trial, to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. During the first year of this award, the trial has successfully opened at the lead site, which is a culmination of FDA IND acceptance as well as scientific and IRB approval. The phase I study is in the second dosing cohort. Thus far the combination of mifepristone and enzalutamide has been well tolerated with no dose limiting toxicities. The current cohort has dose-escalated the enzalutamide and it is anticipated, based on safety and pharmacokinetics that this will be the recommended phase II dose, and that the phase II will start this year.

15. SUBJECT TERMS
Castration resistant prostate cancer (CRPC); Androgen Receptor (AR); Glucocorticoid receptor (GR); Enzalutamide; Mifepristone; Pharmacokinetic (PK) Pharmacodynamic (PD); Prostate specific antigen (PSA)

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1 INTRODUCTION:

This award is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this translational research award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The two major objectives of the award correspond to the two phases of the trial that will be articulated in more detail within the "Accomplishments" section of the report. The first objective is within the context of a phase I clinical trial to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. This will be completed at the lead site. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. This portion of the study will be a multiple-institutions study, lead by the lead site.

2 KEYWORDS

The following are key words that will be used in this report
Castration resistant prostate cancer (CRPC)
Androgen Receptor (AR)
Glucocorticoid receptor (GR)
Enzalutamide
Mifepristone
Pharmacokinetic (PK)
Pharmacodynamic (PD)
Prostate specific antigen (PSA)

3 ACCOMPLISHMENTS:

A. What were the major goals of the project?

As stated in the SOW, the major tasks for the study, with projected timeline are listed as follows. Specific activities accomplished, in concordance with SOW during this quarter will be detailed in the next section.

Major Task 1: Regulatory Approval: Lead and subsidiary sites	**Months 1-6**
Major Task 2: Coordinate and Initiate Phase I Portion of Study	**Months 1-9**
Major Task 3: Complete phase I study	**Months 1-12**
Major Task 4: Initiation of Phase II	**Months 12-15**
Major Task 5: Complete Phase II study	**Months 12-36**
Major Task 6: Data Analysis	**Months 9-36**

B. What was accomplished under these goals?

The following tables summarize the objectives/subtasks to be accomplished during this reporting period specifically, with comments when pertinent.

Major Task 1: Regulatory Approval: Lead and subsidiary sites			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Subtask 1: Obtain Regulatory Approval for Research Protocol at UC: COMPLETE			
Subtask 2: Obtain Regulatory Approval for Research Protocol at PCCTC sites			
PCCTC site identification	1-3	Partial	Trial summary sent to PCCTC sites, several sites interested, one (Oregon) is actively discussing internally, and several waiting until first cohort(s) complete on phase I. Will continue to give progress report to PCCTC sites. Meeting with PCCTC sites in October 2014 at Prostate Cancer Foundation Annual retreat and will discuss trial progress and identify sites at this meetin.
Scientific and IRB submission at PCCTC sites	1-3	No	Sites not committed at this point. Discussions ongoing. Sites wish to wait until phase I complete or near complete.
Coordination of Clinical Trials Agreement (CTA) at PCCTC sites	3-6	Partial	Sites not committed at this point. Discussions ongoing. Sites wish to wait until phase I complete or near complete. However, active central CTA agreements are already in place between the University of Chicago and PCCTC sites.
Scientific Review Approval PCCTC sites	3-6	No	Sites not committed at this point. Discussions ongoing. Sites wish to wait until phase I complete or near complete.
IRB Approval PCCTC Sites	3-6	No	Sites not committed at this point. Discussions ongoing. Sites wish to wait until phase I complete or near complete.

Major Task 2: Coordinate and Initiate Phase I Portion of Study			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Finalization of data capture forms	1-3	Yes	
Site initiation training at UC	1-3	Yes	
Screening and Registration of first patient on phase I at UC	1-3	Yes	

Major Task 3: Complete phase I study	Timeline (months)	Objective complete	Findings, developments, discussion points
Recruitment and enrolment	1-12	Partial	Completed first cohort

PK analysis	3-12	Partial	First cohort PK analysis complete
Weekly institutional data safety monitoring board	1-12	Yes	Ongoing
Monthly safety/oversight teleconference	6-12	NA	Will begin with multi-site participation
Submission of year 1 IND report to FDA	9-12	Yes	
Submission of any protocol amendments to IRB, FDA, HRPO	Continuous	Yes	Personnel and minor clarification ammendments submitted to IRB. No significant changes that mandated HRPO submission
Milestone Achieved: Completion of phase I study	9-12	Partial	

***Note: No items within SOW to be completed on tasks 4-6 during this reporting period**

Discussion of Accomplishments:

Within this reporting period (year 1) there were 3 major tasks to either complete in entirety or begin as listed in the above table. Task #1 was focused on regulatory approval for the clinical trial at the central site (University of Chicago) and at subsidiary sites (TBA). Subtask 1 was to open the trial at the University of Chicago, with full regulatory approval. This has been completed as anticipated and accrual is ongoing. Subtask 2 involved opening the trial at other sites, with multiple sub-objectives outlining this task. This task is not yet complete. The major barrier to this task completion is that other academic sites are not willing to commit to opening the phase II portion of the trial until the phase I portion of the trial is near complete (in the expansion cohort). We have discussed the trial at several PCCTC meeting and have garnered interest in the trial from several sites including Washington University in Seattle, University of Oregon, Dana Farber Cancer Center (Harvard) and Northwestern University. Thus, task 1 completion is dependent on major task 3. In addition to the PCCTC site mentioned, Dr. Stadler, the senior co-investigator for this trial, leads a multi-institution network of regional institutions, "The University of Chicago Personalized Cancer Care Consortium (PCCC)". Should there be insufficient participation within the PCCTC, we can open the trial up to sites within this consortium. Central clinical trial agreements are in existence between the University of Chicago and PCCTC sites as well as the University of Chicago and PCCC sites, which will expedite opening the trial when the phase I is complete (Task 3).

Task 2 is complete with no details to report. Data capture of enrolled patients at the University of Chicago is ongoing without issue. Task 3 is centered around completion of the Phase I clinical trial as described above. Several of the objectives within this task are complete as described within the table. We have accrued 8 and treated patients to the trial and have several other potential patients identified. The first cohort of 6 patients is thus complete and the primary endpoint of this study has been complete for this cohort. Due to safety and PK concerns, the dose of enzalutamide and mifepristone for the initial cohort were conservatively set at 40mg enzalutamide and 300mg mifepristone. The two drugs in combination were well tolerated, with the most common side effect being fatigue (grade 2). There were no grade 3 toxicities nor dose limiting toxicities identified at this dose cohort. The other principal analysis of this task was PK assessment of enzalutamide. We successfully analyzed the drug concentrations of enzalutamide and its active metabolite from our first cohort in collaboration. The drug concentration of enzalutamide for the patients was approximately 50% when dosed in combination compared to

160mg enzalutamide alone. Per protocol guidelines, the current cohort has had the enzalutamide dose doubled to 80mg/day in combination with mifepristone. As cohort 1 PK analysis was 50% lower then full dose, this doubling of enzalutamide we anticipate will be the appropriate dose for the phase II portion of the study. From a PD standpoint, serum cortisol levels were measured before and after mifepristone at 300mg. Cortisol routinely doubled as expected, indicated on target GR antagonism. It is therefore anticipated that 300mg mifepristone is sufficient GR antagonism and that this will be the phase II dose of mifepristone. Thus, to complete Task 3, 4 more patients will be accrued to this cohort, followed by PK analysis. Assuming PK analysis shows appropriate enzalutamide levels as expected, the cohort will be expanded to 12 patient to complete the phase I study. Other sites will be engaged to route to scientific review board and IRB's as in the table at the during this cohort expansion as the recommended phase II dose will be established at this point.

C. What opportunities for training and professional development has the project provided?

This award was not intended for professional development as it is not a training award. Nonetheless, the trial has allowed the PI, a junior investigator, to work as a lead investigator on a complex, multi-site clinical trial. As such provided the PI an opportunity to present trial progress at the PCCTC semi-annual meeting in October 2014. This meeting was attended by representatives from ~15 leading prostate cancer research institutions and included multiple thought leaders in the field. The PI was able to share trial progress and garner support in the group for the trial, which was an excellent learning opportunity.

D. How were the results disseminated to communities of interest?

There were no results to report during this reporting period.

E. What do you plan to do during the next reporting period to accomplish the goals?

The principal goal during the next reporting period is to complete Task 3 (phase I clinical trial) and initiate Major Task 4 (initiation of the phase II portion of the trial). The discussion of Task 3 was detailed above in section 3.B. During the dose expansion of the phase I at the recommended phase II dose, other sites will be finalized for participation so that full accrual to the phase II can begin without any hindrances.

4. IMPACT:

A. What was the impact on the development of the principal discipline(s) of the project?

The clinical trial has not completed and we do not have full results. Therefore, there are no significant impacts to the prostate cancer field as of yet. However, one key impact is that our trial is the first to our knowledge of enzalutamide in combination with another drug that is a pharmacologic inhibitor of enzalutamide metabolism. Enzalutamide metabolism is complex and involved multiple hepatic enzymes. We have shown that a strong inhibitor of CYP2C8/9 and CY3A4 essentially decreases clearance of enzalutamide by half. Beyond our trial, these data may have an impact as enzalutamide is considered in combination with other drugs.

B. What was the impact on other disciplines?

This study is the first study of mifepristone at 300mg daily dosing in an advanced cancer population. GR antagonism is a potential therapeutic maneuver for other

cancers, such as breast cancer. We have shown that daily dosing of mifepristone in patients with advanced cancer is safe. This is impactful as the knowledge of its safety in this population can be used as the drug is developed in other cancers.

C. What was the impact on technology transfer?
Nothing to report

D. What was the impact on society beyond science and technology?
Nothing to report

5. CHANGES/PROBLEMS:

A. Changes in approach and reasons for change
There have been no changes in approach to this research award.

B. Actual or anticipated problems or delays and actions or plans to resolve them
It should be noted that there were barriers to fully accomplishing Major Task 3 during this reporting period. Accrual to the trial was slower then anticipated. We had a verbal agreement with Medivation who were to supply enzalutamide for this trial (Mifepristone is being supplied by Corcept Therapeutics). Rights to enzalutamide in the United States were sold to Astellas, and although Medivation was still in support of the concept, wanted to provide drug, and are supporting the PK analysis still, Astellas refused to provide enzalutamide for the trial, as due to drug-drug interactions, the phase II dose of enzalutamide will likely be lower then the standard dose. Although the FDA label for enzalutamide includes such dose reduction for use in combination with other medications that may inhibit enzalutamide metabolism, Astellas was not willing to assist our trial. As an alternative to enzalutamide being provided by Medivation/Astellas, patients are still enrolling on the trial, but get enzalutamide through their commercial pharmacy. This has slowed accrual as prior authorizations are required and there is often a very high cost to the drug, even with insurance, that has somewhat limited the patient population eligible for the drug. Accrual was also held for ~4 weeks for PK analysis. This was our first PK analysis working with an outside company (InVentiv Health) and it is anticipated that the next cohort analysis will be quicker as all logistics are in place and worked out. The phase I portion of this study is necessarily slow as the dose limiting toxicity period for each cohort is 60 days on trial. Nonetheless we are moving forward with our second cohort, which as stated, will likely define the recommended phase II dose.

C. Changes that had a significant impact on expenditures
Nothing to report

D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Nothing to report
E. Significant changes in use or care of human subjects: Nothing to report
F. Significant changes in use or care of vertebrate animals: Nothing to report
G. **Significant changes in use of biohazards and/or select agents:** Nothing to report

6. PRODUCTS:

A. Publications, conference papers, and presentations: Nothing to report
B. Website(s) or other Internet site(s): Nothing to report
C. Technologies or techniques: Nothing to report
D. Inventions, patent applications, and/or licenses: Nothing to report

E. Other Products: Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

A. What individuals have worked on the project?

Key Study Personnel	Study Roles and Responsibilities	Nearest Person Month, source of funding
Name: Russell Szmulewitz, MD Affiliated Institution: University of Chicago	Study Role(s): Principal Investigator Responsibilities: Study oversight and conduct	2, PC121149 award and University of Chicago internal funds
Name: Elia Martinez, RN, OCN Affiliated Institution: University of Chicago	Study Role(s): Research Nurse Responsibilities: Coordinates research activities for the patients on the study	2, PC121149 award and University of Chicago internal funds
Name: Jeff Bozeman Affiliated Institution: University of Chicago	Study Role(s): Study Coordinator Responsibilities: Data manager for the study	1, PC121149 award
Name: Jaclyn Peterson Affiliated Institution: University of Chicago	Study Role(s): Study Coordinator Responsibilities: Data manager for the study. Took over role from Jeff Bozeman mid-year.	1, PC121149 award
Name: Walter Stadler, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual, research activities and data analysis	0.5 month, University of Chicago internal funds
Name: Peter ODonnell, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Chadi Nabhan, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Mark Ratain Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with data acquisition and analysis	0.5 month, University of Chicago internal funds
Name: Theodore Karrison, PhD Affiliated Institution: University of Chicago	Study Role(s): Biostatistician Responsibilities: Generation of randomization algorithm and assistance with data analysis	1, PC121149 award and University of Chicago internal funds

Name: Sumati Murli, PhD Affiliated Institution: University of Chicago	Study Role(s): Independent Safety Monitor Responsibilities: Oversee study accuracy of interventions, adherence to protocol guidelines, review study recruitment and the weekly data safety monitoring minutes for the trial and coordinate/oversee review of data matching and data collection across the trial.	1, PC121149 award and University of Chicago internal funds
Name: Daniel Bennett Affiliated Institution: InVentiv Health	Study Role(s): Pharmacokinetic laboratory supervisor Responsibilities: oversight and analysis of pharmacokinetic laboratory studies (does not have access to patient identifying information)	1, Medivation Inc

B. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There are two minor changes in personnel on the trial was the change in study coordinator from Jeff Bozeman to Jaclyn Peterson. Jeff left the institution and Jaclyn has taken over as study coordinator and data manager for the trial. The PK analysis is being done at InVentiv Health in Princeton, NJ, not by Medivation, although Medivation is covering the expence. Daniel Bennett is conducting these analyses.

C. What other organizations were involved as partners?

Inventive Health, Inc. is a central laboratory that we have contracted with that is performing the PK analyses embedded within this trial. It is a fee for service agreement with the cost of the analysis being supported through Medivation Inc (Pharmaceutical Company that manufactures enzalutamide).

1. Organization Name: InVentiv Inc.
2. Location of Organization: Princeton, NJ
3. Partner's contribution to the project
    a. Facilities: provide facilities for PK analysis
    b. Collaboration: Samples collected on the trial are sent to InVentiv, who then analyze the samples and provide a report of the enzalutamide and metabolite levels to the University of Chicago.
4. Organization Name: Medivation Inc.
5. Location of Organization: San Francisco, CA
6. Partner's contribution to the project
    a. Financial: provide financial support for PK analysis

8. SPECIAL REPORTING REQUIREMENTS

None

9. APPENDICES

None